1. (3x amended) A method for decreasing cerebral vasoconstriction in a subject suffering from an Alzheimer's disease-type pathology, which comprises administering to the subject an inhibitor of receptor for advanced glycation endproduct (RAGE) in an effective amount to inhibit transcytosis of amyloid-β peptides across the blood-brain barrier in the subject, thereby decreasing cerebral vasoconstriction in the subject.

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REMARKS

Claims 1, 2, 4 and 7-16 are pending and under examination in the subject application. Applicants have amended claim 1 solely to correct a typographical error. Applicants maintain that this Amendment raises no issue of new matter. Accordingly, upon entry of this Amendment, claims 1, 2, 4 and 7-16 will still be pending and under examination.

Pursuant to the requirements of 37 C.F.R. 1.121(c)(1)(ii), applicants annex hereto as **Exhibit A** claim 1 marked up to show the changes made herein relative to the previous version of that claim.

Formalities

The Examiner objected to claim 1 as containing a format informality. Specifically, the Examiner states that the term "vasoconstriction" in line 2 of the claim is misspelled.

In response, applicants have amended claim 1 to correctly spell

the term "vasoconstriction."

Double Patenting Rejection

The Examiner provisionally rejected claims 12-15 under 35 U.S.C. §101 as allegedly claiming the same invention as that of claims 12-15 of copending U.S. Application No. 09/992,955.

In response, but without conceding the correctness of the Examiner's rejection, applicants will consider amending or canceling claims 12-15 once the rejection is no longer provisional.

Obviousness-Type Double Patenting Rejection

The Examiner provisionally rejected claims 1, 2, 4, 7-11 and 16 as allegedly unpatentable under the judicially created doctrine of obviousness-type double patenting over claims 1-11 and 16 of copending U.S. Application No. 09/992,995. According to the Examiner, a timely filed terminal disclaimer in compliance with 37 C.F.R. §1.321(c) may be used to overcome a provisional rejection based on a nonstatutory double patenting ground.

In response, but without conceding the correctness of the Examiner's rejection, applicants will consider submitting a terminal disclaimer for claims 1, 2, 4, 7-11 and 16 once the rejection is no longer provisional.

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1, 2, 4, and 7-16 under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

Applicants respectfully traverse the Examiner's rejection. In support of their traversal, applicants incorporate their remarks regarding enablement made in the October 24, 2002 Amendment and the December 20, 2001 Amendment, and make the following additional remarks to underscore their position.

Claims 1, 2, 4, and 7-11 provide a method for decreasing cerebral vasoconstriction in a subject suffering from an Alzheimer's disease-type pathology, which comprises administering to the subject an inhibitor of receptor for advanced glycation endproduct (RAGE) in an effective amount to inhibit transcytosis of amyloid-β peptides across the blood-brain barrier in the subject, thereby decreasing cerebral vasoconstriction in the subject. Claims 12-15 provide a method for ameliorating neurovascular stress in a subject which comprises administering to the subject an effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE), so as to increase cerebral blood flow in the subject, thereby ameliorating neurovascular stress in the subject. Claim 16 provides a method for treating Alzheimer's disease in a subject who suffers therefrom which comprises administering to the subject an effective amount of an inhibitor of receptor for advanced glycation endproduct (RAGE) activity so as to increase cerebral blood flow in the subject and thereby treat Alzheimer's disease in the subject.

The test for enablement under 35 U.S.C. §112, first paragraph, is whether the disclosure contains sufficient information regarding the subject matter of the claims to enable one skilled in the relevant art to practice the claimed invention without undue experimentation.

The Examiner concedes that the specification is enabling for methods of decreasing cerebral blood vasoconstriction and ameliorating neurovascular stress in a TG APP sw+/- mouse. However, the Examiner asserts that the specification does not enable methods for decreasing cerebral vasoconstriction or ameliorating neurovascular stress in any species other than a TG APP sw+/- mouse (such as humans).

Applicants are not aware of any requirement under 35 U.S.C. §112, first paragraph, that mandates providing human experimental data in the specification in order to enable a claim based on non-human experimental data. Applicants maintain that the disclosed mouse models, which overexpress *human* amyloid beta precursor protein, are an adequate representation of human amyloid angiopathy. Applicants maintain that the data presented in the specification using this model would be expected to correlate with human results.

Applicants therefore assert that human data are not required and that the experimental data disclosed in the subject application are sufficient to enable the pending claims. Indeed, §2164.02 of the M.P.E.P. states that an "in vitro or in vivo animal model example in the specification, in effect, constitutes a 'working example' if

that example 'correlates' with a disclosed or claimed method invention." The Examiner concedes that the instant claims are enabling for the methods of decreasing cerebral vasoconstriction and ameliorating neurovascular stress in a TG APP +/- mouse. Applicants assert that at the very least, these methods and their results in mice would be expected to "correlate" with such methods and their results in humans.

The Examiner further asserts that the specification does not enable the treatment of an Alzheimer's disease-type pathology in any subject.

Applicants respectfully traverse the Examiner's rejection. It is well known in the art that a key component of Alzheimer's disease is the accumulation of amyloid-β peptides (Aβ) in the central nervous system. In fact, a diagnosis of Alzheimer's disease is made only if there is both cognitive degeneration and the presence of senile plaques composed of Aβ peptides in the subject. Applicants have discovered that the RAGE receptor plays an important role in Aβ-mediated uptake at the blood-brain barrier and its transport into the central nervous system. Applicants maintain that based on this discovery and the guidance set forth in the specification, one skilled in the art would know how to practice a method for treating an Alzheimer's disease-type pathology, namely, the inhibition of RAGE-dependent transcytosis of Aβ peptides across the blood-brain barrier. Thus, applicants maintain that the specification is enabling for the instant method of treating an Alzheimer's disease-type pathology.

Accordingly, applicants maintain that claims 1, 2, 4 and 7-16 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Summary

Based on the reasons set forth hereinabove, applicants maintain that pending claims 1, 2, 4 and 7-16 are in condition for allowance. Accordingly, allowance is respectfully requested.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account 03-3125.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

Respectfully submitted,

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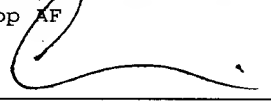

7/12/03

Alan J. Morrison — Date
Reg. No. 37,399

Marked-up Version of the Claims

Additions to the text are indicated by underlining; deletions are indicated by square brackets.

In the claims:

Please amend claim 1 as follows:

1. (3X amended) A method for decreasing cerebral [vasoconstricition] vasoconstriction in a subject suffering from an Alzheimer's disease-type pathology, which comprises adminstering to the subject an inhibitor of receptor for advanced glycation endproduct (RAGE) in an efective amount to inhibit transcytosis of amyloid-β peptides across the blood-brain barrier in the subject, thereby decreasing cerebral vasoconstriction in the subject.